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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/636,001	08/07/2003	Hartmut Strobel	DEAV2002/0058 US NP	1567
5487	7590	03/07/2006	EXAMINER	
ROSS J. OEHLER AVENTIS PHARMACEUTICALS INC. 1041 ROUTE 202-206 MAIL CODE: D303A BRIDGEWATER, NJ 08807			GRAZIER, NYEEMAH	
			ART UNIT	PAPER NUMBER
			1626	
DATE MAILED: 03/07/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/636,001	Applicant(s) STROBEL ET AL.	
	Examiner Nyeemah Grazier	Art Unit 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9 is/are pending in the application.
- 4a) Of the above claim(s) 3, 8 and 9 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2 and 4-7 is/are rejected.
- 7) ☒ Claim(s) 1, 2 and 4-7 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☒ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>11/16/05, 10/3/03</u> | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1626

DETAILED ACTION
FIRST ACTION ON THE MERITS

I. ACTION SUMMARY

Claims 1-9 are currently pending. Claims 3, 8 and 9 are withdrawn from further consideration by the Examiner because Claims 8 and 9 are drawn to a non-elected invention. 37 C.F.R. § 1.142(b).

II. PRIORITY

This application claims the benefit of U.S. Provisional Application Serial No. 60/432,3123 filed on December 10, 2002 under 35 U.S.C. 119(e). Applicant claims priority under 35 U.S.C. 119 (a-d) to foreign application EPO 02017587.3, filed August 7, 2002. However, a *certified* copy of the foreign application has not been received.

III. INFORMATION DISCLOSURE STATEMENT

The information disclosure statements (IDS) submitted on November 16, 2005 and October 3, 2003 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

IV. RESTRICTION/ELECTION

A. Election: Applicant's Response

Applicant's election of Group I, claims 1-6 and the provisional specie election with traverse of the compound of Example 22 in the response filed on January 3, 2006 are acknowledged.

The applicant traverses the restriction on the grounds that the restriction is improper because the inventions are neither independent nor distinct and therefore would not impose a burden on the Examiner. (See Remarks, p. 2 filed January 3, 2006). The applicant also asserts that claim 7 should be rejoined with Group I because claim 7 is a composition claim and not a process of making claim. (Id.).

The abovementioned arguments filed on January 3, 2006 have been fully considered. The argument regarding the rejoinder of claim 7 with Group I is persuasive. Claim 7 directed to an composition and NOT a process of making was previously withdrawn from consideration as a result of a restriction requirement. Claim 7 is hereby rejoined and fully examined for patentability under 37 CFR 1.104. Because a claimed invention previously withdrawn from consideration under 37 CFR 1.142 has been rejoined, **the restriction requirement regarding Claim 7, Group II, as set forth in the Office action mailed on October 6, 2005 is hereby withdrawn.**

In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claims including all the limitations of an allowable product claim or rejoined process claim are presented in a continuation or divisional application, such claims may be subject to provisional statutory and/or nonstatutory double patenting rejections

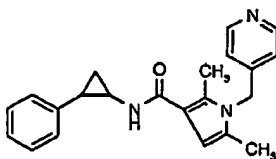
Art Unit: 1626

over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The argument regarding the restriction requirement between the compounds and method of use claims have been fully considered and is not persuasive. The inventions have been shown to be independent and distinct. (See Action filed October 6, 2005, Rationale Section, p. 6). As stated in the Action filed on October 6, 2005 upon determining that the product claims are allowable, the method claims commensurate in scope with the allowable subject matter will be rejoined. (See Action filed October 6, 2005, Advisory of Rejoinder Section, p. 7).

B. Status of the Claims

i. Scope of the Elected Subject Matter



The applicant has elected Example 22, above structure, as the provisional elected specie. The elected subject matter is therefore the compounds and compositions of formula (I) wherein:

n is 1;

R¹ is optionally substituted aryl;

R² is carbon linked pyrrole (at the 3 position) substituted with at the nitrogen with heteroaryl-substituted C1-C4 alkyl.

ii. Extended Prior Art Search M.P.E.P. §803.02

Art Unit: 1626

If upon examination of the elected species, no prior art is found that would anticipate or render obvious the instant invention based on the elected species, the search of the Markush-type claim will be extended. See M.P.E.P. § 803.02 (2001). If prior art is then found that anticipates or renders obvious the non-elected species, the Markush-type claim will be rejected. It should be noted that the prior art search will not be extended unnecessarily to cover all non-elected species. Should Applicant overcome the rejection by amending the claim, the amended claim will be reexamined. Id. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. Id. In the event prior art is found during reexamination that renders obvious or anticipates the amended Markush-type claim, the claim will be rejected and the action made final. Id.

As indicated above, Examiner searched the compound based on the elected species, Example 22, in response to the requirement to restrict the products of Formula (I), wherein: However, there was no prior art of record that anticipated or rendered obvious the elected species and therefore the scope of the subject matter was **extended or broaden** in pursuant to M.P.E.P. § 803.02.

The prior art search was extended to include the compounds of Formula (I) wherein:

n is 1 or 3;

R¹ is optionally substituted aryl;

Art Unit: 1626

R^2 is a 5 membered, monocyclic heteroaryl ring containing at least one nitrogen which is optionally substituted by the following:

halogen, -CN, -NH₂, C₃-C₅-alkandiyl, phenyl, heteroaryl, aryl-substituted C₁-C₄-alkyl, heteroaryl-substituted C₁-C₄-alkyl, -CF₃, -NO₂, -OH, phenoxy, benzyloxy, (C₁-C₁₀-alkyl)-COO-, -S(O)_mR²⁰, -SH, phenylamino, benzylamino, (C₁-C₁₀-alkyl)-CONH-, (C₁-C₁₀-alkyl)-CO-N(C₁-C₄-alkyl)-, phenyl-CONH-, phenyl-CO-N(C₁-C₄-alkyl)-, heteroaryl-CONH-, heteroaryl-CO-N(C₁-C₄-alkyl)-, (C₁-C₁₀-alkyl)-CO-, phenyl-CO-, heteroaryl-CO-, CF₃-CO-, -OCH₂O-, -OCF₂O-, -OCH₂CH₂O-, -CH₂CH₂O-, -COOR²¹, -CONR²²R²³, -C(NH)-NH₂, -SO₂NR²⁴R²⁵, R²⁶SO₂NH-, R²⁷SO₂N(C₁-C₆-alkyl)-,

iii. Non-elected Subject Matter Withdrawn 37 C.F.R. §1.142(b)

The non-elected subject matter is the compounds of Formula (I) wherein:

n is 2 or 4;

R^1 is an optionally substituted heteroaryl;

R^2 is an optionally substituted aryl; an 5 member polycyclic heteroaryl or 5 membered monocyclic or polycyclic heteroaryl containing heteroatoms consisting of O or S; an optionally substituted 6-10 membered monocyclic or polycyclic heteroaryl ring; an optionally substituted C₁-C₁₀ alkyl, optionally substituted C₂-C₁₀ alkenyl, optionally substituted C₂-C₁₀ alkynyl, optionally substituted C₁-C₁₀ alkoxy, optionally substituted C₁-C₁₀ alkylamino, optionally substituted di(C₁-C₁₀ alkyl)amino; a residue of a saturated or partially unsaturated aliphatic monocyclic 5 to 7 membered optionally substituted heterocycle containing 1, 2 or 3 heteroatoms selected from the group consisting of N, O and S.

Rationale:

The Examiner has expanded the search to the point of novelty and has limited the scope to 5-membered ring. (See rejection below). The compounds wherein R₂ can be a 6-

Art Unit: 1626

10 member heterocyclic ring are distinct inventions. For example, formula (I) wherein R2 is pyrazine, for example, are classified in Class 544 while 5 membered rings containing at least one nitrogen are classified in Class 548 and 5 membered ring containing oxygen or sulfur are classified in 549. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

V. REJECTION(S)

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 is ambiguous because it states "A pharmaceutical preparation" but omits steps to the process. Applicant has asserted that claim 7 is a composition claim and not a process claim. (See Remarks, p. 2.). Thus, the claim states a preparation but does not intend to recite a process. Thus, the claim is ambiguous. The applicant can obviate this rejection by deleting "preparation" and inserting "composition."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

Art Unit: 1626

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Atkinson et al. US Patent Pub. No. 2005/049237 (Priority to 60/335958, filed 11/1/01). The reference teaches the compound 1-(4-fluorophenyl)-N-(2-phenylcyclopropyl)-5-(trifluoromethyl)-1H-Pyrazole-4-carboxamide. The compound anticipates the compounds of formula (I) wherein n is 1, R1 is an unsubstituted phenyl, R2 is a 5 membered monocyclic heteroaryl containing two nitrogen atoms substituted by -CF₃, and phenyl; wherein the phenyl substituent on R2 is further substituted by a halogen, namely fluorine. (See U.S. 2005/0049237 A1, p. 27, compound 310).

Claims 1, 2, 4, 6, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by *Biel, et al.* US Patent No. 3,192,229. The reference teaches the compound N-(2-phenylcyclopropyl)-5-methyl-3-isoxazole-carboxamide. (See col. 3, ll. 50-51). The compound anticipates the compounds of formula (I) wherein n is 1, R1 is an unsubstituted phenyl, R2 is an isoxazole ring substituted by -CH₃.

35 USC § 103 - OBVIOUSNESS REJECTION

The following is a quotation of 35 U.S.C. § 103(a) that forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Art Unit: 1626

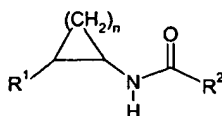
Patentability shall not be negated by the manner in which the invention was made.

Graham v. John Deere Co. set forth the factual inquiries necessary to determine obviousness under 35 U.S.C. §103(a). *See Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Specifically, the analysis must employ the following factual inquiries:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 4, 5, 6, and 7 are rejected under 35 U.S.C. § 103(a) as being obvious over *Atkinson et al.*, US 2005/0049237 A1 (PCT: WO 2003037274 A2). For purposes of the rejection, the US equivalents will be referenced in lieu of the Foreign PCT publication.

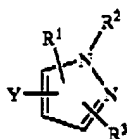
The instant invention recites acylated arylcycloalkylamine compounds and compositions having utility as cardiovascular agents. The compounds allegedly upregulate the expression of the enzyme endothelial nitric oxide synthase. (Spec. p. 1, ll. 21-29). The *provisionally elected* invention is drawn to the formula:



Wherein: n is 1 or 3; R₁ is an aryl group and R₂ is a monocyclic 5 membered heteroaryl group containing at least one nitrogen atom.

The Scope and Content of the Prior Art (MPEP §2141.01)

Atkinson, et al. teaches pyrazole amide compounds and compositions that are useful as sodium channel inhibitors and therefore useful in treating cardiac arrhythmias and neuropathic pain. (*Atkinson, et al.*, p. 1, ¶ [0003]). The invention is represented by the general formula (1):



wherein Y is $-\text{CONR}^4\text{R}^5$ (*Atkinson, et al.*, p. 2, ¶ 0017), R¹ and R³ represent independently hydrogen, C1-C4 alkyl, C3-C7cycloalkyl, C1-C4haloalkyl, C1-C6heteroalkyl, amino, halo, cyano, nitro, hydroxyl, aryl, and heteroaryl (*Atkinson, et al.*, p. 2, ¶0016), R² represents hydrogen, C1-C4alkyl, C1-C7cycloalkyl, aryl, heteroaryl, aryl(C10C4)alkyl or heteroaryl(C1-C4)alkyl (*Atkinson, et al.*, p. 2, ¶0016), R⁴ may represent hydrogen and R⁵ may represent a C3-C7cycloalkyl ring (*Atkinson, et al.*, p. 2, ¶0018) wherein said R⁵ cycloalkyl group may be further substituted with R' wherein R' may be a substituted or unsubstituted aryl. (See *Atkinson, et al.* p. 4, ¶0043). Substituted aryl means aryl substituted by hydrogen, -OR' where R' is hydrogen or alkyl, halogen or -CN, for example. (*Atkinson, et al.*, p. 4, ¶0044).

The Difference Between the Prior Art and the Claims (MPEP §2141.02)

The difference between the prior art of *Atkinson, et al.* and the instant invention is in scope. The prior art teaches a subgenus of the instant invention, namely wherein R² in instant Formula (I) is pyrazole. Both the instant invention and the prior art reference teach compounds, compositions and method of using same for comparable therapeutic uses, such as cardiovascular conditions. Thus, the scope of the claimed subject matter is broader than the prior art.

Resolving Level of Ordinary Skill in the Pertinent Art

The pertinent art is cardiovascular drug discovery and generally medicinal chemistry. One of ordinary skill in the pertinent art of medicinal chemistry, specifically, cardiovascular drug discovery would have the motivation to make and use the instant invention because the abovementioned reference teach compounds useful as sodium channel inhibitors. Sodium channel-blocking agents are effective in treating cardiac arrhythmias. Furthermore, the motivation to make claimed compound derives from the expectation that structurally similar compounds are generally expected to have similar properties and have similar utilities. In re Gyurik, 596 F. 2d 1012, 201 USPQ 552 (CCPA 1979).

Prima Facie Obviousness-The Rational and Motivation (MPEP §2142-2413)

The prima facie case for obviousness is derived from the teaching a specie, compound 310 which anticipates the compounds of the instant invention; and also the preferred teaching of the references. The reference teaches preferred compounds and preferred variable substituents. The “Description of the Embodiment” section sets out the preferred embodiments of the invention. For example, Y is preferably CXNR4R5 where X can be oxygen. (*Atkinson et al.*, p.6, ¶0062). Formula (II) is an exemplary preferred embodiment where R1 and R3 are preferably hydrogen, alkyl and the like, and R2 is preferably aryl or heteroaryl and where X is preferably oxygen. (*Atkinson et al.*, p.6, ¶0064-0065). In another embodiment R4 is C3-C7cycloalkyl and R5 is hydrogen. (*Atkinson et al.*, p.6, ¶0067). Thus, the teachings of *Atkinson et al.* reference would have motivated one skilled in the art to make and use in the instant compounds and compositions with the expectation that they would both have the same pharmacokinetic effect.

Art Unit: 1626

VI. OBJECTION(S)**Claim Objection-Non Elected Subject Matter**

Claims 1, 2, 4-7 are objected to as containing non-elected subject matter. To overcome this objection, Applicant should rewrite instant Claims 1, 2, 4-7 deleting the nonelected subject matter and drawn only the examined elected subject matter.

Dependent Claim Objections

Dependent Claims 2, 4-6 are also objected to as being dependent upon a rejected based claim.

Claim 7 is objected to because of the following informalities: Claim 7 recites “a pharmaceutical preparation.” The claim appears to recite a process of making a composition. Applicant asserts that claim 7 is a composition. To obviate the objection Applicant should reword the claim to read “a pharmaceutical composition.” Appropriate correction is required.

VII. ALLOWABLE SUBJECT MATTER

The allowable subject matter would be the compounds of formula (I) wherein n is 1 or 3; R¹ is an optionally substituted aryl; and wherein R² is a 5 member heteroaryl selected from the group consisting of oxazole, thiazole and pyrrole wherein the heteroaryl may be substituted by:

halogen, -CN, -NH₂, C₃-C₅-alkandiyl, phenyl, heteroaryl, aryl-substituted C₁-C₄-alkyl, heteroaryl-substituted C₁-C₄-alkyl, -CF₃, -NO₂, -OH, phenoxy, benzyloxy, (C₁-C₁₀-alkyl)-COO-, -S(O)_mR²⁰, -SH, phenylamino, benzylamino, (C₁-C₁₀-alkyl)-CONH-, (C₁-C₁₀-alkyl)-CO-N(C₁-C₄-alkyl)-, phenyl-CONH-, phenyl-CO-N(C₁-C₄-alkyl)-, heteroaryl-CONH-, heteroaryl-CO-N(C₁-C₄-alkyl)-, (C₁-C₁₀-alkyl)-CO-, phenyl-CO-, heteroaryl-CO-, CF₃-CO-, -OCH₂O-, -OCF₂O-, -OCH₂CH₂O-, -CH₂CH₂O-, -COOR²¹, -CONR²²R²³, -C(NH)-NH₂, -SO₂NR²⁴R²⁵, R²⁶SO₂NH-, R²⁷SO₂N(C₁-C₆-alkyl)-,

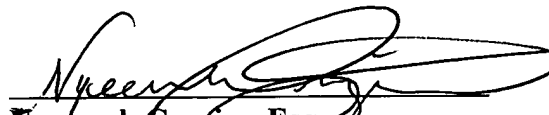
Art Unit: 1626

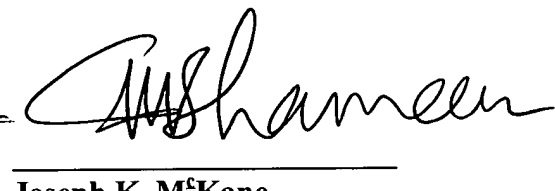
VIII. CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nyeemah Grazier whose telephone number is (571) 272-8781. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:30 a.m. - 6:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached on (571) 272 - 0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Very truly yours,


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